Cancer History: A Predictor of IPMN Subtype and Dysplastic Status?

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Abstract:

Introduction: The aim of this study was to determine the association of PMH and FH of pancreatic (PDAC) and non-pancreatic cancers with IPMN malignant risk.

Methods: A retrospective review of a prospective database of IPMN patients undergoing resection was performed to assess FH and PMH.

Results: FH of PDAC was present in 13% of 362 included patients. Of these, 8% had at least one first degree relative (FDR) with PDAC. The rate of PDAC positive FH in non-invasive versus invasive IPMN patients was 14% and 8%, respectively (p=0.3). In main duct IPMN patients, FH (44%) and PMH of non-pancreatic cancer (16%) was higher than that seen in branch duct IPMN (FH 29%; PMH 6%; p =0.004 and 0.008).

Conclusions: FH of PDAC is not associated with IPMN malignant progression. FH and PMH of non-pancreatic cancer is associated with main duct –IPMN, the subtype with the highest rate of invasive transformation.

Introduction:

Family history (FH) is a key component of clinical history taking due to its well established role in disease development and progression. Specifically, patients with a positive FH for certain cancers are more likely to develop cancer themselves. Cancers such as pancreatic, gastric, and colorectal may be associated with familial syndromes with known genetic mutations, while others, although clearly subject to familial predisposition, have yet to be linked to genetic alterations (1). Up to 10% of patients with pancreatic ductal adenocarcinoma (PDAC) have a positive first or second degree FH for PDAC (2, 3). This high rate of positive FH serves as a useful screening tool for high-risk patients with PDAC. PDAC Five year survival is 8% (4). Although five year survival of localized PDAC rises to 31%, currently only 10% are diagnosed at this early stage (4). Presently, early detection and preventative strategies may offer the best chance for cure. This can only be accomplished with the development of improved prognostic indicators.

In addition to patients with positive FH, patients with pancreatic cysts may be an additional high risk population on which preventative strategies can be effectively employed. Intraductal papillary mucinous neoplasm (IPMN) is a pancreatic cystic neoplasm with variable malignant potential. While well-recognized as a premalignant lesion, it is unclear whether IPMN progression to invasive cancer follows the same course taken in PDAC development. Although IPMN pathogenesis may be distinct from PDAC, previous studies have demonstrated similar associations between IPMN and FH. A multicenter case-control study reported a first degree FH of PDAC in 5% of those with IPMN versus 2% of matched controls ($p<0.01$) (5). Fewer studies attempt to compare rates of positive PDAC FH between patients with invasive versus non-invasive IPMN. Nehra and colleagues compared IPMN patients with and without FH of PDAC

and found no difference in frequency of invasive disease (6). In the current study, we aim to clarify the role of FH and personal past medical history (PMH) of cancer in IPMN malignant progression in order to better define its predictive ability. We hypothesize that patients with a family history of PDAC may be at increased risk for IPMN malignant progression.

Methods:

Patients undergoing pancreatic resection at Indiana University Health University Hospital for IPMN between 1992 and 2015 were retrospectively reviewed using a prospectively collected database. Data were collected and reported in compliance with the confidentiality guidelines defined by the Indiana University Institutional Review Board. Demographic data, and FH/PMH of pancreatic and non-pancreatic cancer were collected from patient electronic medical records. Main duct and branch duct status was defined radiographically as well as pathologically(7). Patients were included if physician clinical documentation contained complete FH data. Format of FH was highly dependent on the author. EMR allows for templated histories, however, documentation outside of templates was common. Many authors specifically note positive vs. negative histories of each cancer type, while others simply state “no family history of cancer.” Pathologic diagnosis including IPMN dysplasia grading and subtype, i.e., main duct versus branch duct involvement, was obtained from final pathology notes. Main duct involved (MD) IPMN included those with main duct and mixed type IPMN. Branch duct (BD) IPMN had no involvement with the main duct. Pancreatic adenocarcinoma in the setting of IPMN high grade dysplasia, or specifically described as “arising from/associated with IPMN” within pathology reports were classified as invasive IPMN. Patients with PDAC and non-contiguous low to moderate grade dysplasia IPMN were not considered invasive IPMN and excluded. Rates of positive FH and PMH of cancer among patients with each level of IPMN dysplasia (low grade,

moderate grade, high grade, and invasive), invasive versus non-invasive IPMN, and MD versus BD IPMN were compared.

Data were collected and analyzed using IBM SPSS (Statistical Package for the Social Sciences) 24. Mean, standard deviation, and frequencies were calculated with descriptive statistics. Continuous data were compared with t-test or ANOVA; categorical data were analyzed with Chi-square test. Multivariate analyses were performed as appropriate. Comparisons with P-values less than 0.05 were considered to be statistically significant.

Results:

Between 1992 and 2015, 428 patients underwent surgical resection of IPMN at Indiana University Health University Hospital. Patients with clearly documented family history (n=362) were included for analysis. Among these, all grades of IPMN dysplasia were represented and included 190 (53%) low grade dysplasia (LGD), 63 (17%) moderate grade dysplasia (MGD), 49 (14%) high grade dysplasia (HGD), and 60 (17%) invasive IPMN. Age and gender were the same between groups (p= 0.08 and 0.2) with 51% male and mean age of 66 years.

Of all IPMN patients, 13% reported a positive FH for PDAC. There was no difference in rate of positive PDAC FH between categories of IPMN dysplasia (LGD: 13%, MGD: 13%, HGD: 20%, invasive: 8%; p=0.3) or between invasive versus non-invasive IPMN (8% vs. 14%, p=0.3). Patients with FH of PDAC were further divided into those with at least one first degree (8%), only second degree (5%), or no relatives (87%) with PDAC. Again, no difference was observed between categories of IPMN dysplasia (**Figure 1**) or invasive versus non-invasive IPMN (p=0.6 and 0.5).

A positive FH of any gastrointestinal malignancy was reported in 21% of IPMN patients, and 53% reported a positive FH of any type of malignancy. However no differences were seen

among groups of IPMN dysplasia (p=0.8 and 0.4). Likewise, no differences were observed when examining rates of FH of only extra-pancreatic malignancy (p=0.5). Degree and number of relatives with gastrointestinal, extra-pancreatic, and all types of malignancy also had no effect on rate of positive FH comparisons. Rates of PMH of any type of malignancy were similar across groups of IPMN dysplasia with 12% overall reporting a positive history (p=0.6).

Similar analyses were then carried out comparing BD IPMN to MD IPMN (**Table 1)**. Although patients with MD IPMN were older (67 vs. 64 years, p=0.01), gender ratio was approximately 1:1 in both MD and BD IPMN (p=0.5). Rate of positive PDAC FH was the same among MD vs. BD IPMN (14% vs. 13%, p=0.8). Analyses considering degree and number of relatives with PDAC revealed similar results with no differences between MD and BD IPMN groups. However, patients with MD IPMN were more likely to report positive FH of non-pancreatic malignancy (52% vs. 40%, p=0.04). This observation strengthened when positive FH included only those with at least one first-degree relative with non-pancreatic malignancy (44% vs. 29%, p=0.004). Rate of positive PMH of non-pancreatic cancers was likewise increased among patients with MD IPMN vs. BD IPMN (16% vs. 6%, p=0.008). Positive FH and PMH of non-pancreatic malignancy were each independently significantly increased in patients with MD-IPMN (p=0.02 and 0.007) in a multivariable regression analysis.

Discussion:

From this large, single-institution, observational, retrospective study of 362 patients with documented FH, we found significant rates of IPMN patients with PDAC FH (13%). However, there was no difference in rates of positive FH of PDAC among patients with differing grades of IPMN dysplasia. Conversely, both FH and PMH of non-pancreatic malignancy were more

common among patients with MD IPMN (higher risk IPMN subtype) as compared to those with BD IPMN.

Based on previously published literature, approximately 14% of patients with IPMN have a relative with PDAC (6). Five to 10% have at least one first degree relative (5, 8). The current study found a similarly high rate of PDAC FH among those with IPMN. Previous reports have further shown this rate to be significantly higher than that of the general population. Capurso and colleagues compared 390 IPMN patients with 390 matched controls and found increased frequency of first degree PDAC FH in IPMN patients (5% vs. 2%) (5). Multiple pathologic studies have reported analogous findings based on comparisons made between pancreas specimens resected for PDAC with and without positive FH (9). Precursor lesions such as IPMN were more commonly identified in specimens of patients with positive PDAC FH (9). Likewise, Canto *et al*. found IPMN in 6 of 78 asymptomatic patients with PDAC FH after undergoing EUS surveillance and subsequent resection (10).

Based on data reported here, IPMN patients with and without FH of PDAC are equally likely to undergo malignant transformation. Few previous studies have examined rates of malignant transformation among IPMN patients with FH of PDAC, but those which exist are supportive of our findings. A Japanese retrospective study of 300 BD and mixed type IPMN patients compared those with and without a first degree PDAC FH. After adjusting for age, no difference in frequency was observed for either PDAC or invasive IPMN (11). Nehra and colleagues similarly reported no difference in prevalence of invasive IPMN between patients with and without PDAC FH among their population of 324 IPMN patients (6).

Interestingly, we found a notable higher rate of MD IPMN among patients with either a FH or PMH of non-pancreatic cancer. As MD IPMN is more commonly associated with invasive

IPMN than BD IPMN, this finding may suggest a need for more intensive surveillance and possibly more aggressive surgical management of MD IPMN patients with FH or PMH of non-pancreatic cancer. Although current literature does not address differences in rate of FH of non-pancreatic cancer between IPMN ductal involvement or dysplasia categories, Lubezky and colleagues compare rates between IPMN and PDAC patients in their retrospective analysis of 82 IPMN patients and 150 PDAC patients (8). They reported increased rates of non-pancreatic malignancy in first degree relatives of those with IPMN over those with PDAC (48% vs 39%).

In regards to PMH of non-pancreatic cancer in IPMN patients, a recent review of the literature included 15 publications covering non-pancreatic malignancy and IPMN (12). Prevalence of non-pancreatic malignancy ranged from 10-38% among IPMN patients, with fourteen of fifteen studies concluding increased prevalence compared to control groups. More relevant to the present study were data comparing PMH of non-pancreatic malignancy of patients with invasive versus non-invasive IPMN. Few studies examined this relationship, finding higher rates of patients with non-invasive IPMN. Authors' speculative interpretation of this finding may also explain the disparity between published data and the present study. Patients with non-invasive IPMN survive longer and therefore have a longer period of time to develop additional malignancies than those with invasive IPMN (12). Studies offering this explanation included follow-up data and so in addition to previous and synchronous malignancies, they were able to include patients with metachronous malignancies. The current study contains only previous and synchronous non-pancreatic malignancy data and thus is not subject to the same survivorship bias.

Limitations of this study include mainly those related to its retrospective nature and method of data collection via electronic medical record (EMR). Data collection was limited by

information available within EMR, which was often incomplete. Clinicians inconsistently document family history. Reports range from a simple “non-contributory” to detailed lists of which specific relatives had what diseases at what age. Prospective study design would eliminate this problem by including detailed data collection templates. Alternately, previous researchers maintained their retrospective design, but contacted all included IPMN patients or next-of-kin to obtain family history retrospectively (8). An additional limitation is one frequently encountered when included patients cover a lengthy time period. The current study spans 23 years, over which time medical record documentation, definitions, and IPMN standard of care have evolved. Furthermore, all IPMN patients included in this study were surgical. Surgeons may have introduced selection bias into this population by having a lower threshold to operate on patients with positive FH.

From these data we conclude, IPMN patients with FH of PDAC do not have increased frequency of invasive disease. However, those with FH or PMH of non-pancreatic malignancy have increased rates of high-risk type MD IPMN. Of note, this data is limited by its retrospective nature and incomplete clinician data entry. Therefore, additional controlled prospective studies are needed to verify our conclusions. Based on these findings, and previous reports, patients with IPMN and FH of PDAC should be considered high risk for the development of cancer, including invasive IPMN, PDAC, and non-pancreatic malignancy. These Patients who do not undergo resection should be closely observed with routine imaging and surgery clinic visits. The first step in application of data presented here is careful documentation of family history for each IPMN patient. Patient counseling should then ensue based on an individual’s specific risk. Depending on risk estimation and patient preference, either surgical resection or intensive surveillance should be pursued.

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Figure 1: Family history of PDAC among patients with IPMN

FH of PDAC was examined among patients with IPMN of varying degrees of dysplasia. Patients were categorized according to degree of dysplasia (x-axis). Rate of positive FH was plotted for each category (y-axis). The blue bars represent rate of no FH, orange bars represent rate of at least one first degree relative, and gray bars represent rate of only second degree relatives with PDAC among each grade of IPMN dysplasia. There was no difference in rate of FH of PDAC between grades of IPMN dysplasia (p=0.6).

LGD/MGD/HGD: low/moderate/high grade dysplasia

PDAC: pancreatic ductal adenocarcinoma

FH: family history

Table 1: MD vs. BD IPMN comparisons

	MD IPMN	BD IPMN	P-value
Age (yrs)	67	64	**0.01**
Gender (% male)	52.2%	48.4%	0.5
FH of PDAC (any relative)	13.8%	12.5%	0.8
FH of PDAC in 1° relatives *	7.0%	9.4%	0.7
FH of non-pancreatic cancer (any relative)	51.5%	40.3%	**0.04**
FH of non-pancreatic cancer in 1° relatives *	43.6%	28.9%	**0.004**
PMH of non-pancreatic cancer	15.6%	6.3%	**0.008**

*FH of PDAC in at least one first degree relative, may also have second degree relatives

MD: main duct involved IPMN

BD: branch duct IPMN

FH: family history

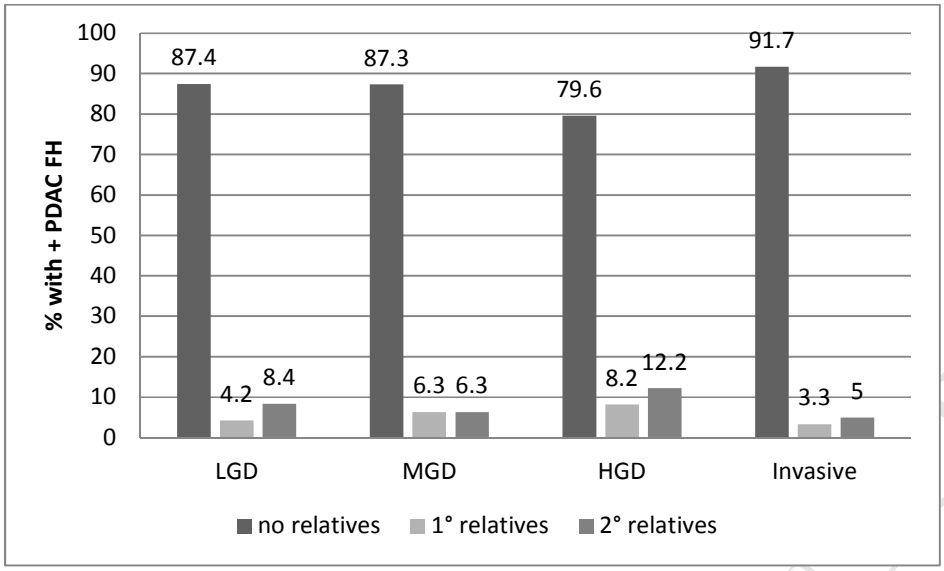
PDAC: pancreatic ductal adenocarcinoma

Keywords:

IPMN, Family History, Pancreatic ductal adenocarcinoma, Past medical history, malignant progression

Summary Sentences:

A retrospective study of IPMN patients was conducted to determine the relationship between family history and past medical history of pancreatic and non-pancreatic cancer, and IPMN malignant progression. Positive family history and past medical history are not associated with IPMN malignant progression. However, in patients with main duct IPMN, family history and past medical history of non-pancreatic cancer was higher than that seen in branch duct IPMN.



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